Summary of Safety and Effectiveness

1. General Information

Trade Name	REVELATION® Tx Microcatheter with NavAblator™ Ablation System
Generic Name:	Cardiovascular Ablation Catheter
Description	REVELATION® Tx Microcatheter / NavAblator™ Catheter Ablation system consists of: ?? REVELATION®Tx Ablation Microcatheter ?? NavAblator™ Ablation Catheter ?? Naviport™ Guiding Catheter ?? REVELATION® Tx SELECT™ Switch Box ?? REVELATION® Tx Cables
Applicant:	Cardima®, Inc. 47266 Benicia Street Fremont, CA 94538 USA Toll Free 888-354-0300 Phone: 510-354-0300 Fax 510-657-4476

PMA #P020039

Date of Panel Recommendation:

Date of notice of approval to the applicant:

2. Indications for Use

The Cardima Inc., REVELATION® Tx Microcatheter RF Ablation System is indicated for the treatment of Atrial Fibrillation in patients with drug refractory paroxysmal atrial fibrillation by creating a set of continuous linear lesions along the lateral and septal walls and along the isthmus in the right atrium.

The REVLATION® Tx is intended for the creation of continuous linear lesions for the purpose of interrupting arrhythmia pathways.

The NavAblator™ is intended for the creation of lesions at the isthmus for the purpose of interrupting arrhythmia pathways when the REVELATION Tx is not used to complete the isthmus region.

The REVELATION Tx and the NavAblator connect to standard mapping/recording equipment and to compatible RF generators with accessory cables and a passive switchbox interface.

The Naviport guiding catheter (an approved device) is intended for access and delivery of the REVELATION Tx to the desired atrial site.

3. Device Description

The Cardima REVELATION® Tx Microcatheter System consists of a single use, steerable, multi-electrode ablation microcatheter (3.7F) with an atraumatic, flexible, non-electrically active tip, and a single use, deflectable NavAblator™ "hot tip" ablation catheter (8F) with an electrically active tip. Accessories to the system include the Cardima Naviport® (a cleared device under K974683), the Tx SELECT™ Switchbox and the associated connecting cables.

The connecting cables and the passive switchbox (Tx SELECT™ Switchbox) are the interface between both ablation catheters and any commercially available electrocardiograph, pacing stimulator and any commercially available endocardial radio frequency generator that is thermocouple compatible.

The REVELATION® Tx catheter has eight flexible electrodes and eight thermocouple temperature sensors in a linear array on the distal end of the catheter. The most distal tip of the catheter is a highly flexible (floppy) non-electrically active platinum coil for fluoroscopic visualization and atraumatic placement. The REVELATION® Tx is designed for the creation of thin linear lesions in the atrium for the treatment of atrial fibrillation by placing the linear array of electrodes along a desired trajectory in the atrium, conforming to the curvature of the wall.

The companion endocardial ablation catheter, the NavAblator™, has four electrodes, one of which is the "hot tip" RF ablation electrode with a thermocouple embedded in its tip.

The NavAblator™ is intended for the creation of lesions (either linear or focal) from its tip when diverse myocardial anatomy requires the features of a "hot tip" ablation catheter to achieve effective lesions.

Both ablation catheters in this system are designed for mapping intracardiac potentials, pacing and ablating cardiac tissue with RF energy.

4. Contraindications, Warnings, and Precautions

Contraindications

?? This procedure is contraindicated in patients with active systemic infection.

?? The catheters in this system should not be used to create lesions in conditions where the catheter would be unsafe (e.g., intracardiac thrombus).

Warnings

?? This device is not intended for ablation from within the coronary vasculature.

?? Use of RF energy may interfere with proper function of pacemakers and implantable cardioverter/defibrillators. Refer to PPM/ICD manufacturer's instruction on use of RF energy with these devices mentioned.

?? Never advance or retract device against unknown resistance or damage to device or its components may occur.

?? Improper handling or use including reuse of this device may result in device failure and/or possible complications.

Precautions

?? Catheter placement should be accomplished under fluoroscopic imaging.

?? The long-term risks of fluoroscopic exposure have not been established.

?? The long-term risks of radiofrequency ablation have not been established.

?? Use in conjunction with the Tx SELECT™ switchbox and Tx Catheter Cable. (See technical specification and requirements)

?? Excessive bending or kinking of the device may cause damage to the device or its components.

?? Always consult the RF-Generator Operating Manual and follow precautions prior to delivery of RF-Energy.

?? The safety and effectiveness of the use of this system in treating children or pregnant women have not been established.

?? This device should only be used by physicians thoroughly trained in the techniques of transvenous intracardiac studies and/or electrophysiology studies.

5. Alternative Practices and Procedures

According to recent ACC/AHA/ESC guidelines, the recommended clinical course for the treatment of Atrial Fibrillation is medical therapy (drugs) intended to first minimize risk of stroke with anticoagulants and second, in more advanced arrhythmias, control heart rhythm by cardioverting (mechanically or pharmaceutically) followed by maintenance of normal sinus rhythm (NSR).

Stroke risk management involves antiplatelet/anticoagulant medication. Heart rhythm management progresses from the use of beta blockers to antiarrhythmic drugs (AADs) that range from Class 1C AADs including propafenone and flecainide, to Class III AADs, including sotalol and Amiodarone that can sometimes precipitate significant side effects, including arrhythmias.

Anticoagulation therapy for stroke risk management requires long-term commitment from the patient for recurring clotting time evaluations and has its own risks associated with increased bleeding.

The antiarrhythmic drugs (AADs) tend to become less effective over time and AF can return in spite of all medications, continuing the risk of stroke and decreasing the quality of life for the patient with AF. In addition, in the presence of heart disease, hypertension or coronary artery disease, AAD therapy faces still further challenges.

Thus, AAD therapy for the management of AF is, at best, palliative. Their ability to maintain sinus rhythm ranges from 39% to 79%. It has been reported for a particular

Canadian patient population that 65% of the patients maintained NSR on Class III agent (Amiodarone) after a mean follow up of 16 months. However, these drugs can be proarrhythmic and organ toxic, precipitating such conditions as Torsade de pointes, ventricular tachycardia, thyrotoxicosis, prostatism and pulmonary and renal toxicity and photosensitivity.

6. Marketing History

The REVELATION® Tx Microcatheter has been approved for commercial distribution in the European Union since November, 1998 and has been distributed in EU countries since that date. This device is also registered for commercial distribution in those other countries that accept EU certification (CE Mark).

7. Potential Adverse Effects

Risks to patients include all those risks currently associated with electrophysiology diagnostic procedures and radiofrequency catheter ablation procedures, such as:

- Bleeding
- Cardiac or vessel wall injury or perforation
- Cerebrovascular accident
- Conduction system abnormalities
- Death
- Hematoma at entry site
- Local or systemic infection
- Pericardial effusion
- Permanent atrioventricular block
- Phrenic nerve damage
- Pneumothorax
- Thromboembolic events

7. Summary of Preclinical Studies

Biocompatibility

The devices were evaluated consistent with the requirements of ISO 10993. The testing demonstrated that the devices that are subject of this submission are biocompatible based upon testing at the Level 1 classification of blood-contacting medical devices.

TEST	SUMMARY OF RESULTS	CONCLUSION
In-Vitro Cytotoxicity	No evidence of causing cell lysis or toxicity greater than mild reactivity	Acceptable
In-Vitro Hemolysis	Mean hemolysis = 0%, 1%, 2% (non-hemolytic = 0-2%)	Acceptable
USP Acute Systemic Toxicity in Mice	No evidence of systemic toxic reaction	Acceptable
USP Intracutaneous Toxicity in Rabbits (Acute)	No evidence of significant irritation or reactivity	Acceptable
Delayed Contact Sensitization in the Guinea Pig (Maximization Method)	No evidence of causing delayed dermal contact sensitization	Acceptable
Thromboresistance in Dog	Minimal thrombus formation, no different than control.	Acceptable
Rabbit Pyrogen Study	No evidence of pyrogenicity	Acceptable
C3a Complement Activation	Lower than "Low biomaterial reference control"	Acceptable

Animal Studies

Cardima conducted four animal studies in support of the safety and performance of the REVELATION® Tx and the NavAblator™. These studies provided evidence of preclinical safety and evidence of the most appropriate system settings to achieve optimal ablation lesions in the right atrium to create a "non-surgical MAZE" approach to treating atrial fibrillation.

Three animal studies of the REVELATION® Tx indicated that the REVELATION® Tx was capable of creating continuous, linear transmural lesions, that a continuous lesion can be formed from sequential electrode ablations; that a set temperature of 50?C-55?C at 35W maximum power output were the best procedural parameters for minimal coagulum formation and optimal lesion formation. These studies also demonstrated that a low pre-ablation pacing threshold was an indicator of good tissue contact and that a large increase in the pacing threshold was a good indicator that lesions had been formed. There were no device-related complications in any of these studies. Further, no correlation between RF energy delivery parameters and lesion size and location could be clearly identified.

In support of the NavAblator™ a study with six dogs was conducted to evaluate the safety and performance of the device when used to create linear lesions in the isthmus of the right atrium, where anatomical challenges may require a "hot tip" device to reach certain areas of the isthmus. The procedural parameter settings used primarily in this study temperature was 60?C for 60 seconds with power output between 25W and 50W.

Device	Study+Objectives	N	Outcome
REVELATION® Tx	Performance of REVELATION® Tx in Right Atrium of Goat. Assessment of device performance, lesion formation and depth with single placement in beating heart of 3 acute and 4 sub-chronic (1-4 weeks) goats. Includes measurement of pacing thresholds, electrogram signal quality and thrombus/coagulum formation.	7	?? No catheter-related complications occurred. ?? Contiguous, transmural lesions were obtained. ?? Thrombus was generally absent on electrodes at 45? and 50?C. ?? An upper power limit of 25W in this study showed good control of thrombus formation.
	Performance of REVELATION® Tx in Right Atrium of Canine. Assessment of deployment, lesion creation and device performance with single placement (no re-positioning) at predetermined locations and predefined control set temperatures in the beating heart of 2 acute and 4 sub-chronic (1 week) dogs. Confirmation of above study in different cardiac morphology.	6	?? No significant catheter placement difficulties in the IVC, SVC, or sub-Eustacian isthmus ?? Contiguous, transmural lesions were obtained in the isthmus with a superior approach. ?? Bipolar and unipolar electrograms were typically of good quality without significant noise. ?? Pacing data confirmed. ?? Small thrombus observed on some electrodes ?? Recommended temp set range (based on this study) is 50?-55?C
REVELATION® Tx	RF Lesion Formation in Canine Thigh Muscle. Assessment of lesion size and thrombus formation in 28 lesions created in 2 dogs	2	?? Continuous lesion was formed from sequential electrode ablations. ?? Thrombus was not observed when 45?C was used, occasionally at50? and 55?C
NavAblator™	Radio Frequency Ablation Using the NavAblater™ for In Vivo Lesion Formation. Assess ability of NavAblator™ to form transmural lesions in the isthmus region of the right atrium, ability to position and map, and a lack of coagulum formation	6	?? No coagulum was observed on the catheter tip following ablation. ?? Pathology reports no pericardial effusion, perforation, thrombus or valvular damage in any of the 6 animals. ?? Pathology confirmed transmural lesions were formed. ?? Unipolar and bipolar electrograms were of good quality, free of noise, and equivalent to those obtained with Cordis-Webster catheter. ?? Pacing threshold was low (<1mA @ 2.0 msec) and was comparable to the Cordis-Webster catheter.

Electro-mechanical Studies

Consistent with the 1995 draft guidance from CDRH, FDA for Cardiac Ablation catheters (Mark Massi, Barbara Zimmerman) performance testing was conducted to demonstrate the reliability and material properties of the REVELATION® Tx and the NavAblator™.

The REVELATION® Tx is not a deflectable catheter nor does it have an open lumen, so joint seal and deflection fatigue testing was not performed. The NavAblator™ does not have a lumen, so joint seal testing was not performed. However, it is a deflectable catheter, so deflection fatigue testing was conducted. The results demonstrate the design of both catheters is robust and consistent with similar devices for similar indications, where comparison can be made. Unlike "conventional" endocardial RF ablation catheters, the REVELATION® Tx has been designed to provide a more flexible and less traumatic interface with endocardial tissue at its distal tip.

The electrical characteristics of the devices were evaluated consistent with IEC 60601-1 and 601-2-2 and found to be compliant with the relevant standards.

The accessory cables and the passive switchbox interface for this system were also tested for reliability and compliance with relevant international standards and found to be compliant. In the case of the switchbox, a third-party evaluation was performed by TÜV Product Services and a certification of compliance was issued.

8. Summary of Clinical Studies

Study Design

The study design is a multi-center, prospective, non-randomized, single-arm, controlled study in which the patients serve as their own control. The “control” is the establishment of a baseline for each patient during a monitoring period in which patients record symptomatic episodes of atrial fibrillation (AF) with portable event monitor cards and transmit these recordings once per week during a 30-day period prior to final determination of eligibility and subsequent treatment. This study design is consistent with

the recommendation for ablation catheter study designs reported by the Circulatory Support Advisory Panel in its meeting of June/July, 1995.

The purpose of the study is to assess the safety and effectiveness of the REVELATION® Tx Ablation System in the treatment of patients with drug refractory paroxysmal AF by creating linear lesions with RF energy in the right atrium.

Patient Assessment

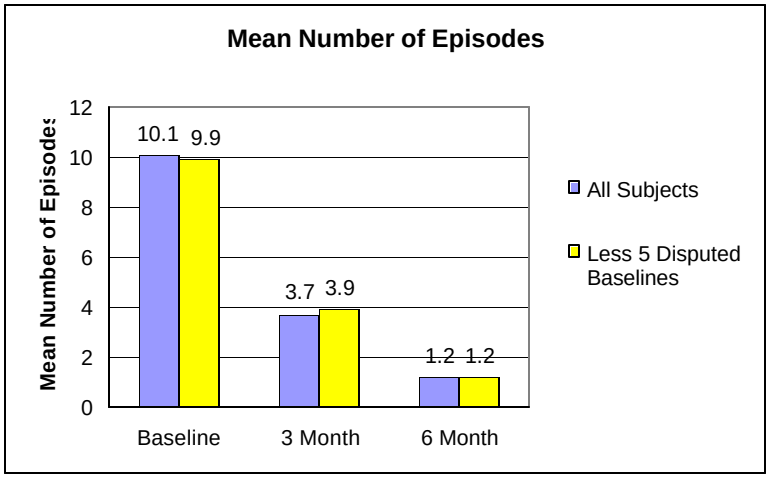
Drug refractory patients with diagnosed paroxysmal atrial fibrillation were assessed prior to treatment to establish a baseline episode frequency of symptomatic atrial fibrillation. Follow up assessments were conducted at one month, three months and six months post ablation for changes in episode frequency, changes in antiarrhythmic medication requirements, general cardiac status and adverse events.

Demographics

Gender	Age in years Mean ? SD	Age Range in Years	Frequency	%
Female	60.7 ± 11.2	27.9?77.1	27	23.3
Male	55.7 ± 10.6	27.6?78.3	89	76.7
Total	56.9 ± 10.9	27.6?78.3	116	100.0

Data Analysis and Result

The results indicate significant reduction in the frequency of spontaneous symptomatic AF episodes experienced by the patients in this study, with an average reduction of 82.9 ± 3.0 with a 3.38% complication rate.



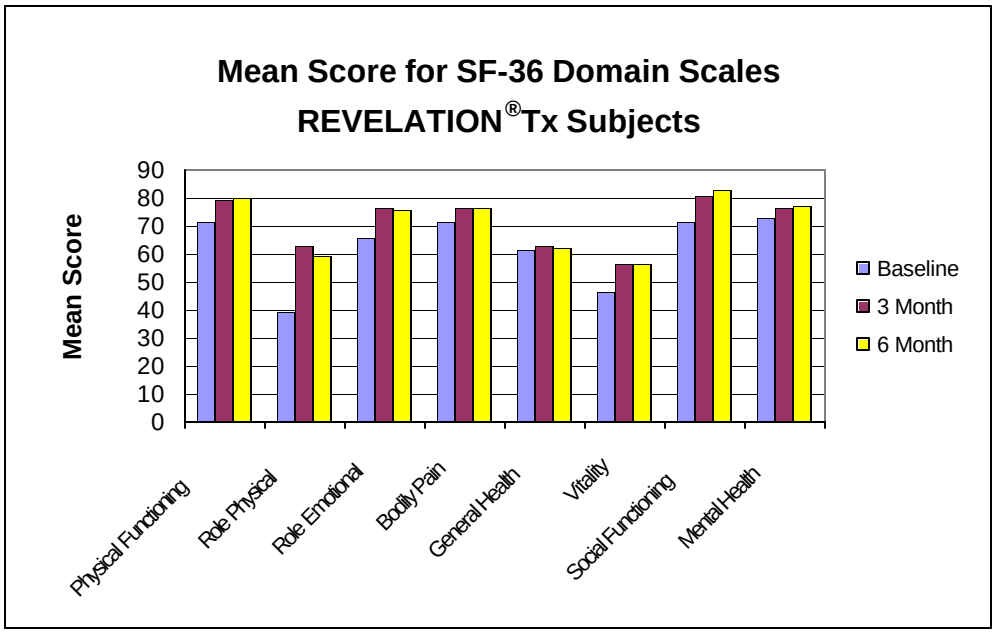
In addition, these patients reported a significant improvement in quality of life, based upon improvements in the scores of the SF-36 and AFSS questionnaires, demonstrating improvement in all eight SF-36 quality of life scales at both the three and six month follow up assessments. There were quite substantial and clinically significant and highly statistically significant improvements for four of the eight domains (Role Physical, Role Emotional, Vitality, and Social Functioning) at both of these follow up assessments, clearly indicating overall substantial patient benefit.

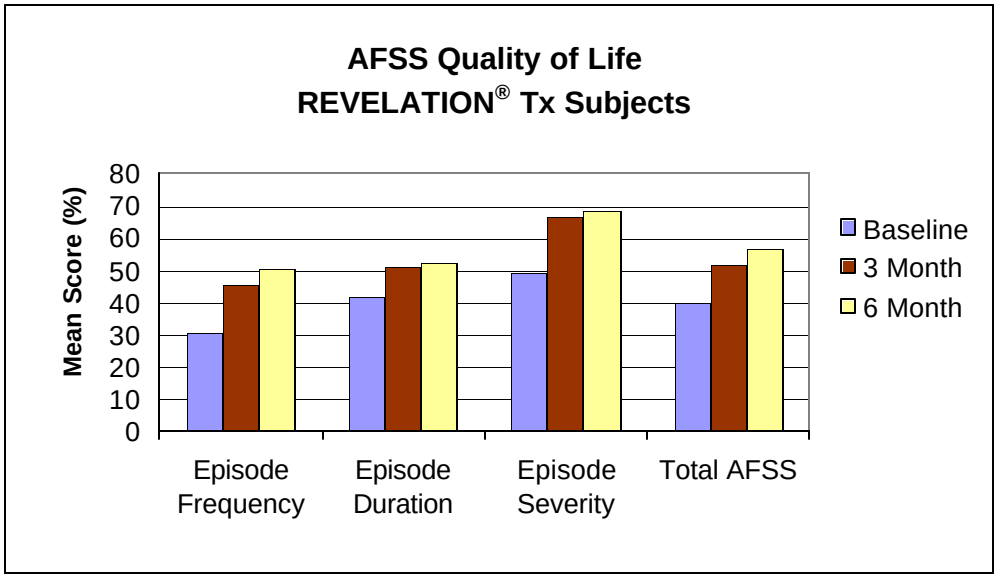
Criteria	**3 Month (n=93) freq/n (%)**	**6 Month (n=81) freq/n (%)**
# of subjects with Episode Reduction compared to Baseline	76/93 (83.9)	79/81 (97.5)
?50% Reduction [a, c]	58/93 (64.5)	69/81 (85.2)
100% Reduction	33/93 (35.5)	44/81 (54.3)
<50% Reduction [c]	33/93 (35.5)[c]	12/81 (14.8)[c]
No Reduction	15/93 (16.1)	2/81 (2.5)
Withdrew	4/93 (4.3)	8/81 (9.9)
Non-Compliant (event monitor)	4	22
Patient not yet at 3, 6 months	12	19
Mean % reduction ± SE	53.1 [b] ± 6.6	82.9 [b] ± 3.0

[a] ?75% for 3-4 baseline episodes [b] p<0.0001

[b] Statistics do not include five subjects with disputed numbers of baseline episodes.

[c] Includes those with "no reduction" as a subset of the <50% reduction group. In the >50% reduction group, those with 100% reduction are included.


Mean Score for SF-36 Domain Scales
REVELATION®Tx Subjects
Mean Score
90
80
70
60
50
40
30
20
10
0
Physical Functioning
Role Physical
Role Emotional
Bodily Pain
General Health
Vitality
Social Functioning
Mental Health
Baseline
3 Month
6 Month


AFSS Quality of Life
REVELATION® Tx Subjects
Mean Score (%)
80
70
60
50
40
30
20
10
0
Episode Frequency
Episode Duration
Episode Severity
Total AFSS
Baseline
3 Month
6 Month

Device Failures and Replacements

There were no device failures or replacements in this study.

9. Conclusions Drawn from the Studies

Risk/Benefit

Risks to include all those risks associated with all electrophysiology diagnostic procedures and radiofrequency catheter ablation procedures. The risks of the procedure are related primarily to mechanical injury to the heart and vessels from catheter manipulation and thermal injury due to RF current delivery, including the risk of thromboembolism and myocardial infarction. The standard risks of anesthesia also exist and include allergic reactions, medical complications and death.

Benefits for drug refractory patients are the potential for reduced symptoms of AF without the adverse effects of the drugs or with a reduced dependency on the medication, for an improved quality of life.

Safety

Major complication rate associated with this study were 3.4%. A small number (53) of minor complications associated with this study occurred in 26% of the subjects (31/115) and were largely mild and transient in nature, related to the cardiac catheterization procedure and not the devices. There were no deaths associated with this study.

Effectiveness

The study demonstrated that the majority of the patients treated in this study reported a statistically and clinically significant reduction in the frequency of AF episodes and similar improvements in quality of life.

The results of these studies have demonstrated the safety and effectiveness of the Cardima REVELATION® Tx Ablation System.

10. Panel Recommendations

11. CDRH Decision

Approval Specifications